CHAPTER 1

PHYSIOLOGICAL, ECOLOGICAL, AND EVOLUTIONARY BASES FOR THE AVOIDANCE OF CHEMICAL IRRITANTS BY BIRDS

LARRY CLARK

1. INTRODUCTION

The chemical senses in birds are only infrequently considered. This dearth of general appreciation of avian chemical sensory systems is understandable. Vision, audition, tactile, and thermal sensory systems have readily quantifiable stimuli and relatively few mediating receptor systems. In contrast, chemical signals are mediated by numerous sensory systems, the stimuli themselves are myriad, and the method by which the stimuli reach the receptor systems can at best be described as chaotic. Nonetheless the chemical senses are critical to the survival and feeding ecology of species. Recent reviews have described the functional and adaptive aspects of avian olfactory and gustatory systems (Waldvogel, 1989; Kare and Brand, 1986; Berkhoudt, 1985; Bang and Wenzel, 1986; Wenzel, 1973). This review considers the least generally

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understood chemical sensory system of birds, the avian trigeminal system.

The majority of the chemical senses of birds fall into three categories: olfaction (smell), gustation (taste), and chemesthesis (irritation/pain). The presumed adaptive value of chemically sensitive systems, in terms of food acquisition and ingestion, is to provide proximal information regarding nutritive, caloric, and toxic potential. Other chemically sensitive systems exist in birds, but will not be considered here, e.g., bill tip organ of Anseriiformes and the nervus terminalis (Wenzel, 1973).

Olfaction acts as a telereceptive system, capable of receiving airborne chemical stimuli in extreme dilution over relatively great distances. Olfactory receptors are located in the nasal conchae. Odors are received through the nares during respiration, and they then pass over the olfactory epithelium (Bang and Wenzel, 1986). Except for Kiwis (*Apteryx* spp.), birds do not sniff (Wenzel, 1968). Therefore, obvious olfactory sampling behaviors are absent in birds. Nonetheless, olfaction is important to their evaluating the palatability of food. Volatiles from food held in the mouth travel retronasally to the nasal conchae and to the olfactory receptors. Although the matter once was controversial, recent research indicates birds have an adequate sense of smell (Waldvogel, 1989; Bang and Wenzel, 1986; Wenzel, 1973), with avian olfactory ability reflecting the anatomical and performance diversity seen in mammals (Clark *et al.*, 1993). Olfaction has been implicated as a navigational aid (Walcott, 1996; Walraff 1991), as a means of locating food (Bang and Wenzel, 1986), and as a sense used in the identification and exploitation of plants useful as antiparisitical and antimicrobial agents (Clark, 1991).

Gustation requires a more intimate contact between the source of the chemical signal and the receptors. Gustatory receptors are located in taste buds throughout the oral cavity. For humans, the sensations of taste are restricted to assessment of sweetness, sourness, saltiness, and bitterness (Burgard and Kuznicki, 1990; Kare and Brand, 1986). Not all species perceive all these taste qualities, but taste among species is generally limited to these qualities. Sensitivity among birds to "tastants" reflects species-specific ecologies and food habits and follows the same patterns seen in mammals (Berkhoudt, 1985; Kare and Rogers, 1976; Gentle, 1975; Kare and Ficken, 1963; Engelmann, 1934; Rensch and Neunzig, 1925).

Chemesthesis is reserved for nonspecific stimuli that are often irritating or painful, i.e., for chemically nociceptive stimuli. Parker (1912) suggested that the function of the common chemical sense was to signal

the presence and amount of noxious chemicals via a unimodal system. Subsequent studies showed that, unlike gustation and olfaction, coding for noxious chemicals is not organized under one sensory nerve, or in one region of the skin. Although all skin is sensitive to a greater or lesser extent to chemical irritants (Keele, 1962), chemical sensitivity to irritants is not the major function of the primary sensory afferents of the skin. For example, a major component of the common chemical sense is the trigeminal nerve (TN). The TN is the principal somatosensory nerve of the head (Getty, 1975), and its primary function is the coding of mechanical and thermal stimuli involved in feeding (Gottschaldt, 1985; Zweers *et al.*, 1977; Zeigler *et al.*, 1975). However, the trigeminal nerve also contains fibers that mediate the detection of noxious chemicals (Gentle and Hill, 1987; Silver and Maruniak, 1980). The somatosensory system is the primary somatic sensory system of the rest of the body. Like the TN, the somatosensory system primarily codes for mechanical and thermal stimuli, but it does have sensory afferents that are chemically sensitive (Szolscanyi, 1990; Kitchell and Erikson, 1983).

Emphasis in describing responsiveness to chemical stimuli has been placed principally on taste and smell. However, caution must be exercised in referring to chemical stimuli as exclusively olfactory, gustatory, or chemesthetic in nature. The sensory afferents of the TN and olfactory nerves (ON) are in close proximity in the nasal cavity, and the TN and gustatory nerves are in close proximity in the oral cavity. Most chemicals can stimulate multiple sensory afferents, although circumstances may favor detection by one sensory system over others. The term "flavor" is reserved for the integrated perceptual qualities of food, which for intact animals are composed of gustatory, olfactory, and chemesthetic qualities. Except in studies of ablation, electrophysiology, or neural membrane permeability, in which specific nerve function in response to specific chemical stimuli can be documented, attributing specific sensory mediation of a chemical stimulant is not possible.

In Section 2, I begin with a general anatomical description of the chemesthetic system of birds and proceed to the neurochemical mechanisms mediating the perception of irritation and pain (Section 3). In Section 4, the chemical nature of chemesthestic stimuli is considered as well as the evidence for the role of the different sensory systems in mediating avoidance response. In Section 5, the taxonomic differences between birds and mammals in chemical irritation are considered, and an example of how plants may exploit such differences is presented. I also consider the importance of the chemical nature of repellents in fruits and how it may influence potential seed dispersers' ability to learn about the palatability of the fruits (Section 6). Finally, in Section

7, I consider how a detailed knowledge of mechanism of repellency can be used to develop tools for the conservation and management of birds.

2. ORGANIZATION OF CHEMESTHETIC PATHWAYS

Birds and mammals appear to have similar superficial structure and function of chemically receptive neurons. The discharge patterns and conduction velocities of chemically sensitive fibers of the trigeminal and somatosensory systems for the chicken (*Gallus gallus*), Mallard (*Anas platyrhynchos*), and Rock Dove (*Columba livia*) are similar to those of mammals (Gentle, 1989; Necker, 1974). These afferents are primarily unmyelinated, C-type, polymodal nociceptors with conduction velocities of 0.3–1 m/sec. Some myelinated A-delta, high-threshold, mechanoreceptors with conduction velocities of 5–40 m/sec also will respond to chemical stimuli. Optical microscopy indicates that bundles of unmyelinated fibers discard their perineural sheath and splay out in a manner consistent with the description of free nerve endings in mammals (Kruger and Rodin, 1983).

The TN is the Vth cranial nerve arising from the rostrolateral medulla near the caudal surface of the optic lobe (Getty, 1975; Schrader, 1970). TN travels along with the trochlear nerve (IVth cranial nerve), entering a fossa in the floor of the cranial cavity where the trigeminal ganglion (TG) is found. TG is subdivided into a smaller medial ophthalmic region and a larger lateral maxillomandibular region from which the nerve splits into three branches. In the chicken, the ophthalmic branch of the TN innervates the frontal region, the eyeball, upper eyelid, conjunctiva, glands in the orbit, the rostrodorsal part of the nasal cavity, and the tip of the upper jaw. The ophthalmic branch has a communicating ramus with the trochlear nerve, which serves for motor control of the eye region. This aspect can provide for reflexive response to irritating stimuli to the ocular region. The larger medial ramus accompanies the ON into the nasal fossa via the medial orbitonasal foramen. The maxillary branch of the TN provides sensory input from the integument of the crown, temporal region, rostral part of the external ear, upper and lower eyelids, the region between the nostrils and eye, conjunctival mucosa, the mucosal part of the palate, and the floor and medial wall of the nasal cavity. The mandibular branch of the TN provides sensory input from the skin and rhamphotheca of the lower jaw, intermandibular skin, wattles, oral mucosa of the rostral floor of the mouth, and the palate near the angle of the mouth. Several studies have elucidated the sensomotor aspects of the trigeminal system (Woolley

and Gentle, 1987; Zeigler, 1973; Ziegler *et al.*, 1969; Zeigler and Witkovsky, 1968).

Somatosensory afferents project through the spine along a number of ascending pathways, leading ultimately to the brain (Willis, 1983). The medial group consists of the spinoreticular system, propriospinal system, and paleospinothalamic tract and is phylogenetically conservative in its development among vertebrates. Afferents of the medial group contribute to the sensation of persistent pain associated with tissue damage, and stimulation of these tracts leads to behavior that promotes healing, e.g., inactivity. Afferents of the lateral group, which consists of the neospinothalamic tract and the spinocervical tract, show more species specificity in extent of development and structure (Mehler, 1969, 1957). The lateral-group afferents contribute to the sensory discrimination of pain, i.e., qualitative, temporal, and topographic aspects (Melzack and Casey, 1968), and stimulation of these tracts leads to active avoidance behaviors.

3. NEUROCHEMICALS CODING FOR PAIN AND IRRITATION

Nociceptors are specialized neurons that provide animals with information about the noxiousness of chemical, mechanical, and thermal stimuli. Because nociceptors provide an animal with information about tissue damage, or the threat of damage, they arguably serve an adaptive function. Noxious chemical stimuli may give rise to different qualitative perceptions, depending upon the nature of the activating stimulus. For example, animals possess a variety of neurochemicals that code for different qualities of noxiousness (Jessell and Kelly, 1991; Terenius, 1987). Stabbing, throbbing, burning, and itching are examples of perception of nociceptors activated by specific neurochemicals when tissue damage occurs. The cell damage results in the release of peptides [e.g., bradykinin, substance P (SP)], amines (e.g., serotonin, histamine), arachidonic acid derivatives (e.g., prostaglandins), and acetylcholine. The threshold for tolerance of nociceptive signals, mediated by the central nervous system, dictates the perception of whether or not a noxious stimulus is painful. An animal's willingness to tolerate pain is subject to its motivational state (Melzack, 1973).

The underlying physiological and biochemical processes mediating nociception appear to be similar for birds and mammals (Figure 1). Neurochemicals such as bradykinin, SP, serotonin, and acetylcholine evoke pain-related behaviors in chickens, Rock Doves, and guinea pigs (*Cavia* spp.) (Gentle and Hunter, 1993; Gentle and Hill, 1987;

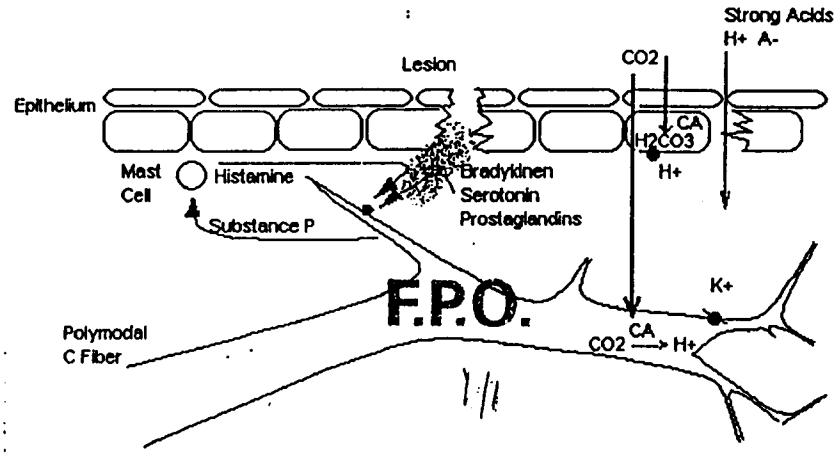

FIGURE 1. A schematic representation of the routes of stimulation for a C-type polymodal nociceptor. Bradykinin, serotonin, prostaglandins, and histamine are endogenous neurochemicals that interact with specific receptors on the nociceptor to evoke a response. Substance P (SP) is released from stimulated nociceptor fibers, and interstitial SP stimulates mast cells to release histamine. CO_2, K^+, and H^+ may cause the nociceptor to respond directly.

Szolcsanyi *et al.*, 1986). Prostaglandins, which modulate the pain response in mammals, also do so in birds (Clark, 1995; Macari *et al.*, 1993). In European Starlings (*Sturnus vulgaris*) as in mammals, the effects of prostaglandins can be abolished by prostaglandin biosynthase inhibitors, i.e., aspirin-like analgesics (Clark, 1995).

Sensations of irritation and pain resulting from exposure to exogenous chemicals, i.e., plant metabolites and insect defensive secretions, can be mediated in any of three ways (Nielsen, 1991). First, chemical irritants may act nonspecifically by causing physical damage to cells, thus setting forth a release of neurochemicals that activate specific pain receptors (Figure 1). Second, chemical irritants may trigger a neurogenic response by nonspecifically activating the free nerve endings of the nociceptive receptors via proximal electrostatic or charge activation, i.e., they induce proton flow across cation channels initiated by physical proximity of the stimulus to the receptor, but they do not require direct mediation by a receptor structure. Third, chemical irritants may evoke a nociceptive response by specifically binding to and activating chemical receptors on the sensory afferent.

Exogenous chemicals often produce primary nociceptive responses (irritation or pain), but may also give rise to secondary nocicep-

tive responses (reddening or inflammation). Curiously, both these forms of nociceptive response are often produced without causing tissue damage. Rather, the exogenous compounds cause the release of neurochemicals by nonspecific or receptor-mediated activation of the nociceptors, thus "fooling" the animal into perceiving physical damage to tissue when in fact there is none. Furthermore, many plant and insect chemical defenses may quite effectively mimic the neurochemicals used by animals to warn of physical danger and damage. This is known as the neurochemical mimicry hypothesis.

4. CHEMICALS AS CHEMESTHETIC IRRITANTS AND REPELLENTS

Primary repellents are compounds that produce an avoidance response immediately after exposure. Such responsiveness does not require learning (Figure 2; Rogers, 1974). For ingestive behaviors, avoidance is typically characterized by reduced food or fluid intake. However, repellency does not imply a specific mechanism mediating avoidance.

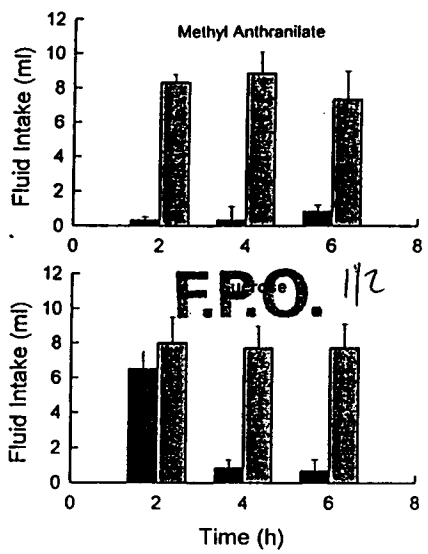

FIGURE 2. Top panel shows the effect of a primary repellent on avoidance of treated fluid as a function of time. Black bars depict intake by a group of European Starlings presented with fluid containing methyl anthranilate (1% wt/vol); grey bars depict water intake by a control group. Typically for primary repellents, the intake of methyl anthranilate is low and constant over time. Bottom panel shows the effect of a secondary repellent on the avoidance response as a function of time. Black bars depict intake by a group of European Starlings presented with sucrose solutions (40% wt/vol); grey bars depict intake for the control (water) group. Typically for secondary repellents, the initial consumption is high initially, then decreases. In this case the diminution of consumption over time is a learned avoidance of the sweet taste of sucrose (conditional stimulus) owing to the post-ingestional gastric illness resulting from the starlings' inability to digest sucrose (unconditional stimulus). Vertical capped bars depict one standard error. (Adapted from Clark and Mason, 1993.)

Indeed, avoidance might be mediated by any sensory modality or combination of modalities, e.g., olfaction (Mason and Clark, 1996b), taste (Kare and Ficken, 1963), or chemesthesis (Clark, 1996). Secondary repellents are avoided because an animal associates an aversive experience, e.g., illness or pain, with a sensory stimulus; thus, learning is required (Zahorik, 1976). For situations involving ingestive behavior, a synonym for this response is conditioned flavor or taste avoidance (Evans, 1985; Garcia *et al.*, 1966). Birds can be trained to avoid otherwise innocuous cues, e.g., tastes (Schuler, 1983), odors (Clark and Mason, 1987), and visual cues (Mason and Reidinger, 1983; Brower, 1969), when these cues are paired with an illness-producing agent. Understanding the mechanism underlying the avoidance response and identifying the sensory system that contributes to that response are important to understanding the chemical ecology of plant–animal interactions (Section 6) and to developing appropriate formulations and delivery strategies for wildlife management tools (Section 7).

4.1. Anatomical and Behavioral Evidence for Irritants as Repellents

Early investigations found that food treated with any of a variety of anthranilates is avoided by birds. Anthranilates are ester derivatives of 2-amino benzoate. Much of the work in this area focused on the avian repellent properties of methyl anthranilate (Clark *et al.*, 1991; Mason *et al.*, 1989; Kare, 1961). To humans, methyl anthranilate has a grape- or fruitlike odor, and at high concentrations (10,000 ppm) it is perceived as both irritating and bitter. The question whether the repellency of methyl anthranilate to birds is attributable to taste, odor, irritation, or some combination was unanswered until recently.

The earliest mechanistic studies concluded that avian avoidance of methyl anthranilate is mediated by taste centers in the brain. Brain regions identified as taste centers were inferred based on projections of nerves innervating taste buds, e.g., chorda tympani and the lingual branches of the glossopharyngeal nerve (Kitchell *et al.*, 1959). When presented with small beads, chicks innately peck at the objects. The pecking response is suppressed if the bead is painted with methyl anthranilate (Lee-Teng and Sherman, 1966). Avoidance of treated beads is unlearned and persists as long as the compound is present. When the taste centers of the brain are lesioned chicks fail to retain the avoidance response (Salzen and Parker, 1975; Benowitz, 1972; Mark and Watts, 1971; Watts and Marks, 1971; Lee-Teng, 1969; Lee-Teng and Sherman, 1969). Thus, the avoidance of beads coated with methyl anthranilate

was presumed to be attributable to the chemical's unpalatable taste qualities. One difficulty in the interpretation of these studies is that the brain regions identified as taste centers, e.g., neo- and archistriatum, also receive projections from the sensory trigeminal system (Zeigler *et al.*, 1969). Thus, these regions can be interpreted as feeding centers, but the importance of gustation and chemesthesis to the response cannot be separated.

If volatiles are important in generating the avoidance response, then the role of olfaction and chemesthesis must be accounted for. The role of chemesthesis in the avoidance response can be ascertained by manipulation of TN sensory input. Chemesthetically mediated avoidance could be attributable to direct contact and stimulation of nerves in the oral cavity, or to exposure of nociceptive fibers in the eye and/or oral–nasal cavities to volatiles.

Birds can detect volatiles, and they can be trained to avoid them (Henton, 1969; Henton *et al.*, 1966; Michelsen, 1959). However, unconditioned avoidance occurs at high concentrations (>10% vapor saturation; Keverne *et al.*, 1986; Silver and Maruniak, 1980; Tucker, 1971, 1963) and requires stimulation of the ophthalmic branch of the trigeminal nerve (OBTN; Walker *et al.*, 1986, 1979; Mason and Silver, 1983). Starlings with the OBTN intact, but with the ON transected, continue to avoid food treated with coniferyl benzoates, which are aromatic compounds with structural properties similar to the anthranilates (Jakubas *et al.*, 1992). Conversely, when the OBTN is cut and the ON is left intact, avoidance of coniferyl benzoates is lost.

The role of chemesthesis as the primary sensory modality for the repellency of anthranilates is also illustrated in a study by Mason *et al.* (1989). Starlings given bilateral ON transects required slightly higher concentrations of anthranilates before they rejected treated food, suggesting that olfaction contributes to the avoidance response, but does not drive it. Curiously, in a separate study Clark (1996) found that in the absence of oral contact olfaction has no modulatory effect on consumption. Bilateral transection of the ON as well as OBTN resulted in a substantial increase in anthranilate concentrations required for rejection of treated food, indicating the importance of trigeminal mediation for the avoidance response (Figure 3), and also the importance of the interaction between chemesthetic and olfactory systems when stimuli are presented orally (Mason *et al.*, 1989). It is not surprising that the avoidance response was not completely eliminated. Mandibular and maxillary branches of the TN were left intact. These branches of the TN, and possibly the gustatory nerves, contributed to the remaining, substantially diminished, avoidance response.

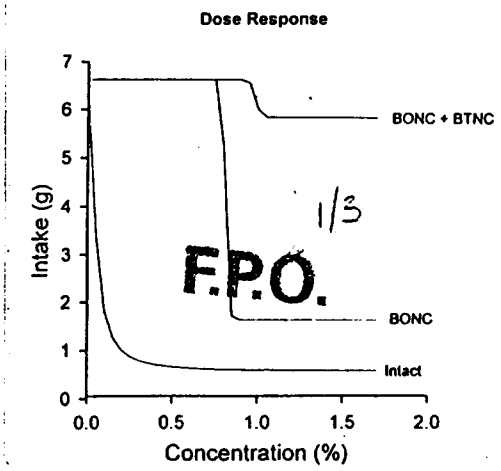

FIGURE 3. Idealized dose–response curve of food intake (grams) by European Starlings as a function of surgical manipulation of chemosensory systems. Food was treated with the primary bird repellent methyl anthranilate. The surgical manipulations were Intact, a sham surgical condition in which all chemosensory systems were left intact; BONC, in which birds were subjected to a bilateral olfactory nerve cut; and BONC+BTNC, in which birds were subjected to a bilateral olfactory nerve cut and a bilateral nerve cut of the ophthalmic branch of the trigeminal nerve. Right and upward shifts of the curves indicate lower sensitivity to the irritant. The curves show the greater importance for trigeminally mediated chemical signals to the avoidance response relative to olfactory cues. Curves were generated from data presented in Mason *et al.* (1989).

Lesion studies are subject to some criticism, because nerve cuts can influence behavior beyond that anticipated by investigators (Wenzel, 1974). For example, animals receiving olfactory nerve cuts not only lose their sense of smell, but may become hyperactive. Such animals are generally more proficient in active avoidance tasks, but they are less proficient in passive avoidance tasks. These nonolfactory consequences on animal behavior arising from olfactory lesions and cuts may decrease food consumption, because the animal spends less time feeding owing to its hyperactivity; this could be interpreted mistakenly as a decreased sensitivity to an olfactory or trigeminal stimulus (Wenzel and Salzman, 1968). I do not consider decreased food consumption attributable to hyperactivity to be a reasonable interpretation of the starling data of Mason *et al.* (1989), because the baseline food consumption and, by implication, a measure of activity are similar across all surgical treatments (Figure 3). Thus, I interpret the avoidance response as being mediated by the sensory properties of the stimuli and not a function of nonchemosensory consequences of surgical manipulation.

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If volatiles are important in generating the avoidance response, then the role of olfaction and chemesthesis must be accounted for. The role of chemesthesis in the avoidance response can be ascertained by manipulation of TN sensory input. Chemesthetically mediated avoidance could be attributable to direct contact and stimulation of nerves in the oral cavity, or to exposure of nociceptive fibers in the eye and/or oral–nasal cavities to volatiles.

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Oral delivery of repellents does not necessarily imply that receptors in the oral cavity of birds mediate the avoidance response. Indeed, the oral cavity is impervious to many irritants. Tight junctions between cells prohibit access of many compounds to the free nerve endings of trigeminal nociceptors. For example, birds are unaffected by oral exposure to nonvolatile pain-promoting neurochemicals, e.g., bradykinin, acetylcholine, serotonin, prostaglandins (Gentle and Hill, 1987; L. Clark, unpublished). However, pain responses can be elicited by these neurochemicals if lesions in the oral cavity are present. Other nonvolatile compounds may also mediate avoidance without involving gustatory receptors. For example, quinine hydrochloride is readily rejected by pigeons when presented orally (Duncan, 1960), despite a lack of electrophysiological evidence that gustatory nerves are involved in mediating the signal (Landolt, 1970; Kitchell *et al.*, 1959). In this case, permeability of the agent through the integument allows it to come in contact with nociceptive free nerve endings. Together, these observations suggest that aromatic irritants achieve sufficiently high concentrations only when presented orally and that avoidance is mediated by retronasal stimulation of nociceptors located in the nasal capsule. For humans the most familiar example of this mode of stimulation is the burning sensation experienced after eating horseradish.

4.2. Pharmacological Evidence

Pharmacological evidence indicates that in starlings avoidance of acetophenones is mediated by the chemesthetic system. The repellent effect of acetophenones is enhanced when starlings are treated with prostaglandins (Clark, 1995). Prostaglandins are modulators for the perception of pain and irritation in mammals and birds (Kotwani *et al.*, 1994; Ferreira, 1972). When prostaglandin biosynthesis is blocked by analgesics, the sensitivity of starlings to acetophenones is diminished (Clark, 1995).

4.3. Other Aromatic Bird Repellents as Irritants

The nerve-cut studies on o-amino acetophenone, anthranilates, and coniferyl benzoate provide clear evidence of chemesthetic mediation of the avian avoidance response. However, the role of chemesthesis in mediating avoidance of other aromatic repellents is largely inferential, based upon structural similarities of stimuli to the above compounds and similarities of timed food/fluid intake assays.

Birds typically sample small quantities of foods/fluids treated with primary repellents (i.e., those causing irritation or pain), but the amount sampled over time remains relatively constant. This pattern of consumption stands in contrast to the pattern of consumption observed for secondary repellents (i.e., those where a learned association between repellent and illness or injury occurs). For example, birds will consume similar quantities of treated material and control substance, indicating initial indifference to the flavor cues of the repellent (Figure 2). In the case where the target repellent is both the unconditional and conditional stimulus, the consumption of treated material, e.g., sucrose consumption by starlings, will fall dramatically as a function of time (Clark and Mason, 1993).

I have tested 117 aromatic compounds and, based upon their structural similarity to anthranilates and acetophenones and the patterns of consumption, I inferred that the mode of action for avoidance is probably chemesthetic in nature (Clark, 1997a). Empirically, the following patterns emerge for the aromatic compounds tested (Figure 4; Clark, 1997a): The strongest repellents are aromatic heterocycles containing nitrogens and simple acetophenone structures. Aromatic N-heterocy-

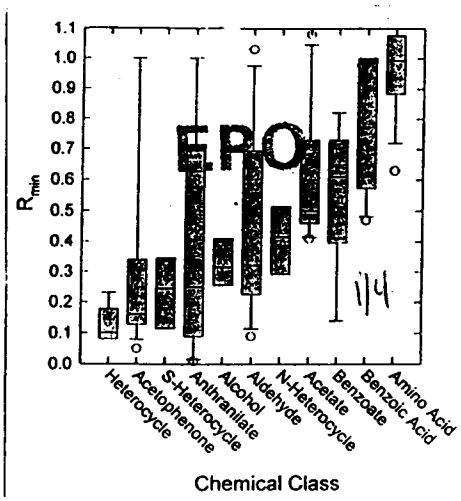

FIGURE 4. The average relative fluid intake of repellents by European Starlings as a function of chemical class of aromatic structures. R_{min} is an individual's consumption of treated fluid divided by its pretreatment water intake. Some amino acids were preferred to plain water solutions, thus yielding an R_{min} greater than 1.0. The ranking of the median avoidance for each chemical group corresponds to the qualitative structure–activity model proposed by Clark and Shah (1991b; also see text). The variation about the mean response reflects the substituent groups included in the analysis, i.e., the degree to which such groups were electron-withdrawing or -donating, position of the substituent, and the planarity of the molecule. Horizontal solid lines depict mean R_{min}. The vertical shaded boxes depict the 75th percentile for R_{min}. The vertical capped bars depict the 95th percentile for R_{min}. The circles depict the maximum and minimum values falling outside the 95th percentile range. (Adapted from Clark, 1997a.)

cles are more uniformly repellent than are acetophenones. Compounds derived from S-heterocycles, anthranilates, aromatic alcohols, and aromatic aldehydes tend to be moderately good repellents. Birds that consume alcohols show signs of toxicosis; thus, these compounds are not strictly primary repellents. Anthranilates and aldehydes result in a high degree of variability for activity. Benzoic acids are not, as a class, good repellents. Amino acids are not repellent.

4.4. Chemical Structure–Activity Relationships as a Mechanistic Basis for the Peripheral Mediation of Primary Repellents

Topology, electrostatic properties, charge distributions, and physicochemical attributes of aromatic chemical structures have been studied for their effects on the primary avoidance response in birds (Clark, 1997a). Other structures also have been considered on a case by case basis (Clark and Shah, 1994, 1991a; Crocker *et al.*, 1993; Avery and Decker, 1992; Crocker and Perry, 1990; Mason *et al.*, 1989; Kare, 1961). Together these studies have led to a hypothesis about the structure–activity relationships of avian repellents (Clark and Shah, 1991a).

The empirical properties of classes of bird-repellent compounds were discussed above. The general features of aromatic bird repellents are as follows. The aromatic parent structure, i.e., an unsaturated five- or six-carbon ring, is critical for repellency (Clark and Shah, 1994). Factors that affect the delocalization of lone pairs of electrons around the aromatic structure contribute to modifying the repellent effect. Acidic substituents to the benzene ring generally detract from repellency, and this effect is amplified if the acidic function is contained within the electron-withdrawing group. Electron donation to the benzene ring enhances repellency. Substituents that contribute to basicity of the molecule (e.g., amines, methoxy groups) contribute to potency. Heteroatoms that distort the plane of the aromatic structure tend to lessen repellency, whereas factors that strengthen planarity (e.g., H bonds, covalent heterocycles) tend to increase repellency (Clark and Shah, 1994, 1991a; Shah *et al.*, 1992, 1991; Clark *et al.*, 1991; Mason *et al.*, 1991a). The qualitative model for identifying primary aromatic bird repellents has held up well (Clark and Shah, 1994, 1991a), and a quantitative model for predicting the parameters of dose–response curves of primary repellents has proved useful (L. Clark and E. Aronov, unpublished). The consistency of the results suggests an underlying general mechanism mediating responsiveness to avian primary repellents that we believe to be chemesthetic in nature.

5. TAXONOMIC DIFFERENCES IN RESPONSIVENESS TO CHEMICALS AS IRRITANTS

5.1. Avian Insensitivity to Capsaicin

Capsaicin is a naturally occurring vanillate and the major pungent constituent found in the fruit pulp of red pepper (*Capsicum* spp.) (N. Jancso *et al.*, 1967). Mammals respond to acute, local, or systemic capsaicin exposure with strong nociceptive reactions (e.g., pain and inflammation), neurogenic edema, and loss of thermoregulatory ability (Fitzgerald, 1983). Chronic topical exposure to capsaicin leads to heightened sensitization and increased pain perception, followed by desensitization (Green, 1990; Szolcsanyi, 1990). Because of its effects on mammals, capsaicin has become an important probe for elucidating mechanisms of pain, inflammation, and thermoregulation. Other compounds with similar structural features have been used for this purpose as well. Resiniferatoxin is a phorbol-related diterpene found in latex of *Euphorbia* spp. and is a potent functional analog of capsaicin. Resiniferatoxin is three to four orders of magnitude better than capsaicin in producing thermoregulatory deficits and inflammation, but has about the same effect for producing acute pain in mammals. Resiniferatoxin contains a 4-hydroxy-3-methoxyphenyl substituent that is critical for capsaicin activity in mammals (Maggi *et al.*, 1990; Szallasi and Blumberg, 1989).

Despite capsaicin's widespread effectiveness as a mammalian chemical irritant, it has virtually no effect on birds (Geisthovel *et al.*, 1986; Szolcsanyi *et al.*, 1986; Pierau *et al.*, 1986; Mason and Maruniak, 1983). Parrots (*Amazona* spp.; Mason and Reidinger, 1983), Rock Doves (Szolcsanyi *et al.*, 1986), Red-winged Blackbirds (*Agelaius phoeniceus;* Mason and Maruniak, 1983), European Starlings (Mason *et al.* 1991a), House Finches (*Carpodacus mexicanus;* Norman *et al.*, 1992), and Cedar Waxwings (*Bombycilla cedrorum;*, Norman *et al.*, 1992) are indifferent to foods treated with ≥1000–20,000 ppm capsaicin. Mammals typically avoid much lower concentrations of these substances; a concentration of 100 ppm capsaicin is avoided by rodents. Mammals are 2500 times more sensitive than birds to arterial injections of capsaicin and 1000 times more sensitive to eye instillation (Szolcsanyi 1985, 1984; Andoh *et al.*, 1982; Crayton *et al.*, 1981; Baraz *et al.*, 1968).

Substance P (SP) is a neurotransmitter released from sensory afferents, and it acts in a positive feedback loop to sensitize the primary afferents in both taxa (Fields, 1987; Gentle and Hill, 1987; Lembeck and Gamse, 1982). When capsaicin is applied to spinal slices in mammals,

SP is released (Gamse *et al.*, 1979). This is not the case for Rock Doves (Pierau *et al.*, 1985). Similar results are seen for gut sensory afferents when capsaicin is injected subcutaneously (Ball, 1985).

Chronic topical application of capsaicin to peripheral nerves of mammals decreases sensitivity to noxious stimuli (Abbott *et al.*, 1984; Fitzgerald and Woolf, 1982; G. Jancso *et al.*, 1980), but it has no effect on Rock Doves (Sann *et al.*, 1987). Furthermore, topical peripheral exposure to capsaicin leads to accumulation of SP in the dorsal horn (Sann *et al.*, 1987), whereas it is depleted in rats (Gamse *et al.*, 1982; Ainsworth *et al.*, 1981). Because birds and mammals share mechanisms for neurotransmitter modulation of the pain response, these observations suggest that the peripheral receptors involved for capsaicin detection are less numerous in birds, or that they have a lower affinity (Sann *et al.*, 1987).

The indifference that birds exhibit toward at least some mammalian irritants reflects both relative insensitivity and a high tolerance for these substances, independent of sensation (Mason and Clark, 1995a). With training, European Starlings will respond to high capsaicin concentrations, although not as irritants. Curiously, an intact trigeminal nerve is important for acquisition of this learned response (Mason and Clark, 1995b). This suggests that starlings detect capsaicin via trigeminal chemoreception just as mammals do (Silver *et al.*, 1985). The surprising difference between the taxa is that the mammalian trigeminal system appears to encode capsaicin as a chemically painful stimulus, while the avian trigeminal system does not.

5.2. Avian Insensitivity to Other Mammalian Chemical Irritants

Although the morphological organization of the peripheral trigeminal system in birds is not very different from that found in mammals (Dubbeldam and Karten, 1978; Dubbeldam and Veenman, 1978), profound functional differences appear to exist (Norman *et al.*, 1992; Mason *et al.*, 1991b). In addition to the taxonomic differences in responsiveness to capsaicin, birds rarely avoid other mammalian irritants, even though the avian trigeminal system is responsive to chemical stimuli (Clark, 1997a; Mason and Silver, 1983; Walker *et al.*, 1979). Rock Doves, Red-winged Blackbirds, European Starlings, and Gray Partridges (*Perdix perdix*) are indifferent to ammonia (Mason and Otis, 1990; Soudek, 1929), though geese (*Anser* spp.) are sensitive to this mammalian irritant (Callahan *et al.*, 1974). Red-winged Blackbirds and European Starlings are indifferent to 1000 ppm gingerol and zingerone,

the mammalian irritants present in ginger (*Zingiber officinale*), as well as to 1000 ppm piperine, the active ingredient in black pepper (*Piper nigrum*; Mason and Otis, 1990).

Changes in carbon dioxide concentration in the nasopharynx region can cause species-specific changes in reflexive breathing in birds (Hiestand and Randall, 1941). However, concentrations of carbon dioxide that are sufficiently high to be irritating to mammals have no effect on blood pressure, heart rate, tidal volume, breathing frequency, upper airway resistance, or lower airway resistance in geese (*Anser anser* and *Cygnopsis cygnoid*; Callanan *et al.*, 1974). Similarly, geese respond differently than mammals to exposure to sulfur dioxide (Callanan *et al.*, 1974).

5.3. Basis for Perceptual Differences between Birds and Mammals

The studies by Sann *et al.* (1987) suggest that differences between birds and mammals for sensitivity to chemicals as irritants are attributable to differences in receptor mechanism. This interpretation is consistent with results of studies of structure–activity relationships of avian and mammalian repellents. The mammalian capsaicin receptor is hypothesized to consist primarily of two sites: a benzene moiety site that is associated with a thiol/hydrogen-bond donating site. This latter site reacts with the C–C double bond and hydrogen bond acceptor site on a stimulus molecule, allowing the aromatic substituent to interact with the benzene moiety site on the receptor (Szolcsanyi and Jancso-Gabor, 1973). Interaction with the thiol site is presumed to be critical for activation of the benzene site (Figure 5). Thus, long-chain alkyl and aromatic OCH_3 and OH are critical features of the mammalian capsaicin receptor (Szolcsanyi, 1990). In contrast, capsaicin and its analogs do not influence avian behavior. However, vanillate derivatives that lack the long alkyl chain, an OH substituent on the phenyl ring, or an attached carbonyl functionality are good avian repellents (Figure 6; Shah *et al.*, 1991). These observations suggest that the thiol site is absent in birds and that activation of the benzene site is achieved by other means. The unidentified ancillary site would interact with the electron-donating group in bird repellents, either as a hydrogen donor or electrostatic attraction. Thus, the difference between the mammalian capsaicin receptor and the proposed avian methyl anthranilate/o-amino acetophenone receptor may simply reflect the loss of expression of the putative thiol site in birds (Clark and Shah, 1994).

An alternative explanation for the observed differences between birds and mammals in sensitivity to exogenous compounds may reside

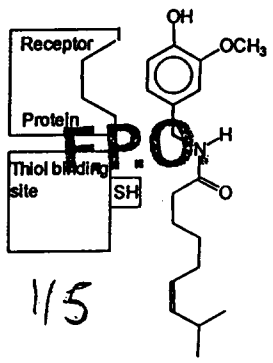

FIGURE 5. A schematic representation of the mammalian nociceptive vanillate receptor proposed by Nielsen *et al.* (1991). The C–C double bond in the capsaicin stimulus molecule's alkyl chain would interact with the thiol-binding site. Activation of this site would result in a conformational change in the receptor protein, exposing the binding site for benzene moieties. Birds also possess a benzene moiety site. However, it appears that the thiol-binding site is absent and replaced with a conformation of charged surfaces (Clark and Shah, 1994). This proposed minor difference in vanilloid receptor structure has profound consequences for the sensitivity of each of these taxa to various aromatic structures: each is largely sensitive to a different aromatic chemical class of compounds as trigeminal irritants.

in structural differences of the epithelium overlying the nociceptive free nerve endings, or in permeability characteristics of the mucous and/or integument layer. This hypothesis is testable. Recent advances in cell culture techniques will enable investigators to grow chemically sensitive nociceptors *in vitro*. Because activation of such cells corre-

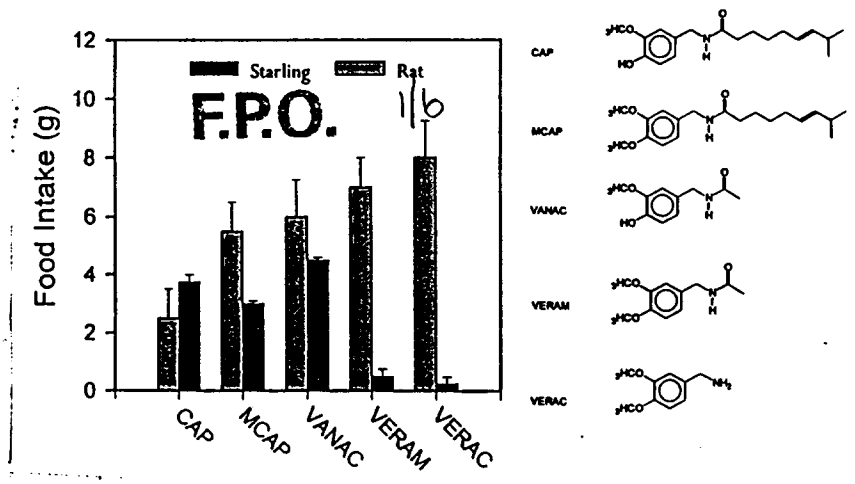

FIGURE 6. Food intake of different aromatic compounds by laboratory rats and European Starlings, illustrating the taxonomic difference in sensitivity to various substituent structures. Compounds that are good repellents for the rat are not so for the starlings, and vice versa. Structures that are good mammal repellents are less electron-rich on the aromatic ring structure. The potential stearic effects of the alkyl structure are mitigated by the thiol-binding site in the mammalian receptor protein. Codes for compounds are capsaicin (CAP), methyl capsaicin (MCAP), vanillyl acetate (VANAC), veratryl amine (VERAM), and veratryl acetate (VERAC). (Adapted from Mason *et al.*, 1991a.)

sponds to influx of calcium ions, histochemical or phosphorescent imaging techniques can be used to determine taxonomic specificity (or nonspecificity) of exogenous compounds as chemical irritants. Regardless of the mechanism underlying the differences in irritant perception in birds and mammals, the fact that differences do exist has profound implications for foraging decisions made by species in these taxa.

6. ECOLOGICAL AND EVOLUTIONARY IMPLICATIONS

6.1. *Capsicum* Plants

The selective argument underlying the poor responsiveness and apparently low sensitivity of birds to mammalian irritants remains obscure. Indeed, the differences may simply reflect phylogenetic accident, i.e., the chance fixation of a mechanism during the evolution of these taxa. However, these differences suggest possibly adaptive defensive strategies for plants. For example, *Capsicum* species may exploit the fundamental differences in sensory systems of birds and mammals (Mason *et al.*, 1992, 1991a) by selectively repelling mammalian seed predators but not avian seed dispersers (Norman *et al.*, 1992). Vanillate aromatic amides are present only in the red, upright fruits and nowhere else in the *Capsicum* plant. The fruits themselves are high in vitamins, proteins, and lipids (Herrera, 1987), traits that are correlated with avian dispersal (Willson and Hoppes, 1986; Willson and Thompson, 1982). Birds are commonly seen feeding on wild capsicum fruits, colloquially known as "bird peppers." Rodents have not been observed eating these fruits, although they will readily consume *Capsicum* spp. seeds in the absence of capsaicinoids (D. Norman, unpublished observations). *Capsicum* possess a chemical defense that deters potential seed predators (rodents), but is undetectable by potential seed dispersers (frugivorous birds; Mason and Clark, 1995a, b). The plants may also gain further selective advantage because capsaicin is an antimicrobial (Duke, 1987). Thus, fruits can persist longer and seeds are protected until dispersal.

The selective consequences for ignoring the chemical defense by mammals are unknown, but the following possibility suggests itself. Capsaicin is poorly absorbed in the gut. Indeed, the persistent irritating qualities of capsaicin are well described by the Hungarian saying that "capsaicin is the spice that burns twice" (Rozin, 1990). Although neurotoxic to mammals when injected systemically, capsaicin is not toxic when ingested or topically applied. Nevertheless, capsaicin does have a negative effect on mammals. Initially it produces nociceptive pain, but

without any other physiological consequences. Acute exposure is generally sufficient to dissuade most mammals (except humans) from voluntarily continuing ingesting material containing capsaicin (Rozin, 1990). Indeed, capsaicin will sensitize mammals to the further effects of capsaicin in the short term (i.e., within minutes). However, under chronic exposure, capsaicin will eventually deplete SP, and physiologic and behavioral desensitization will occur. Chronic exposure of mammals to capsaicin also results in desensitization to the neurochemicals bradykinin, acetylcholine, and histamine. Desensitization to other exogenous irritants also occurs, e.g., to piperine, zingerone, and mustard oil (Szolscanyi, 1990, 1988, 1977; Toth-Kas *et al.*, 1986; Szolscanyi *et al.*, 1985; Carpenter and Lynn, 1981). Because capsaicin is a good antagonist of nociceptive neurochemicals, it may increase the chances that a desensitized mammal will experience increased tolerance thresholds for pain, resulting in increased risk of physical injury. Also, because capsaicin desensitizes mammals to other exogenous compounds, a mammal may increase its risk of ingesting not only noxious doses, but possibly toxic doses, of plant defensive compounds. No such effects are observed in birds. Indeed, besides the nutritional rewards of *Capsicum* fruits, it has been observed that fowl fed chronic diets containing capsaicin are resistant to *Salmonella enteritidis* infection (McElroy *et al.*, 1994; Tellez *et al.*, 1993). Thus, *Capsicum* species may have evolved a general mammalian and insect seed defense mechanism that is irrelevant to potential avian seed dispersers.

6.2. Relationship between Toxicity and Innate Avoidance

A common belief among biologists is that the congenital perception of a compound as unpalatable is an evolutionarily adaptive response that protects an animal against the toxic potential of that compound. The relationship between toxicity and palatability of alkaloids is frequently cited in support of this hypothesis (Cheeke, 1989, 1976; Mattocks, 1986); alkaloids are often toxic and they are often perceived as bitter. Despite the intuitive appeal of this hypothesis, there is little systematic evidence to support it. Indeed, the two studies that systematically examined the dependence of palatability on toxicity of chemicals failed to find any relationship. Glendenning (1995) did not find a relationship between toxicity of alkaloids and palatability. Using Red-winged Blackbirds, European Starlings, and Japanese Quail (*Coturnix coturnix*) as models, Schafer *et al.* (1983) failed to demonstrate a relationship between toxicity and repellency among 998 chemically diverse compounds. Nonetheless, the absence of a statistical relationship

between toxicity and palatability does not mean that compounds are not avoided on the basis of their sensory qualities. Avoidance of odor, taste, and visual cues is largely owing to a learned avoidance response (Mason, 1989; Clark and Mason, 1987; Guilford, 1987; Riley and Tuck, 1985; Brower, 1969) rather than a congenital predisposition to avoid particular visual or flavor cues. In cases in which a chemical is both the unconditional (UCS) and conditional stimulus (CS), the salience of a sensory attribute of a chemical as a CS in the development of the learned avoidance response is directly related to its illness-producing potential (UCS) (Riley and Tuck, 1985; Pelchat *et al.*, 1983).

In contrast to taste and odor cues, the dose-dependent avoidance of irritants is a congenital response, i.e., initial avoidance is not learned. Indeed, because many irritants can cause tissue damage, it is reasonable to suppose that the congenital avoidance of these chemicals is an evolved adaptive response, albeit indirectly so. For those chemicals that cause damage to tissues the perception of irritation or pain is mediated via the release of endogenous neurochemicals for which the animal has specific receptor mechanisms (Figure 1). In this instance the chemically induced damage is really no different than mechanically induced damage. Even for those irritants that are avoided at concentrations below levels for which tissue damage occurs one might argue that the hypersensitivity is an evolved defensive mechanism that minimizes the risk of tissue damage or toxicosis. This interpretation assumes that multiple receptor mechanisms have evolved to recognize potentially harmful compounds and implies that the diversity of receptor mechanisms is adequately matched to recognize the myriads of potentially harmful exogenous chemicals.

Another plausible interpretation for hypersensitivity to irritants derives from the fact that many exogenous irritants function as agonists to the neurochemicals that code information about tissue damage in animals. The effect of these exogenous chemicals is to promote the perception of tissue damage irrespective of whether or not such tissue damage might actually occur. Thus, the congenital avoidance of irritants should not be interpreted as an adaptive recognition of the toxic potential of these compounds. Rather, avoidance is based on a mimicry system. This interpretation shifts the evolutionary adaptation from target species to the organisms producing the defensive chemicals. Unlike toxicants, which tend to be species-specific, irritants tend to be broadly active across species within a taxonomic group. Thus, compounds that activate chemically sensitive receptor mechanisms in one species within a taxon are likely to be active against other species within that same taxon (Mason *et al.*, 1991b). It is not necessary that these defensive

chemicals share similar topologies to activate the few receptor types responsible for coding information about irritation and pain. Vastly different structures may still possess similar electronic and electrostatic properties necessary for activation of a receptor (Lipkowitz and Boyd, 1990). Thus, the myriads of defensive irritant compounds produced by different plants and insects may reflect not only species' biosynthetic constraints based on topology, but also a convergent evolution on the functional (e.g., electrostatic or electronic) form of a defensive molecule.

If there has been a quantum mechanical convergence of defensive compounds to match the receptor mechanisms for trigeminal and somatosensory chemoreceptors, then what prevents vertebrates from evolving discriminatory sensory systems to recognize neurochemical mimics? I suggest that the evolution of such a recognition system is too costly because it requires fundamental changes in taxonomically conserved neurotransmitter function. If this is true, then why are not such mimetic defense systems more prevalent and infallible as chemical defenses? I suggest that the answer lies in how such defenses are delivered against their target, the potency of the chemical as an unconditional stimulus, and the ability of an animal to learn about the conditional stimulus. These issues are addressed in the following subsection.

6.3. Preventing Untimely Frugivory: A Hypothesis

The maturation of fleshy parts of fruits roughly coincides with the maturation of the seed. From the plant's perspective, untimely frugivory occurs when potential dispersal agents remove the fruits prior to the full maturation of the seed. Plants can promote frugivory by providing potential dispersal agents with an energetic enticement in the form of sugars and other nutrients. Plants can limit frugivory by withholding energetic rewards and/or by presenting chemical defenses to potential dispersal agents. In the latter case, the chemical nature of the defense will profoundly influence the type and level of protection.

Although toxicity may not be inherently coded by the sensory attributes of a molecule, animals can readily learn about the toxic effects of compounds if the nature of the toxicity and chemical signal are salient. As previously discussed, secondary repellents can yield strong learned aversions. However, the localization of the negative effect is critical. In the case of toxicosis, the strongest learned aversions are formed when illness is localized in the duodenal region of the gastrointestinal system (Pelchat *et al.*, 1983). This is the site of potentially high absorption of nutrients and, by inference, the site yielding the highest

risk of transporting toxicants systemically to the individual. Once a pairing of an illness and sensory cue occurs, the individual easily generalizes the cue to similar sensory cues (Palmerino *et al.*, 1980).

In contrast, primary repellents may not be suitable as general unconditional stimuli. For example, starlings avoid a variety of aromatic irritants upon first exposure, but fail to learn to associate the negative attributes of irritation with odor or visual cues (Clark, 1996). Two important facts may explain this failure of primary repellents to act as general unconditional stimuli. First, the negative consequence of the irritant may be limited because its effect is localized in the oral/nasal cavity, i.e., peripherally. Second, the dose and, by implication, the extent of irritation are self-limiting. The result is that animals stop behaviors that expose them to the irritant before strong and sustained painful sensory experiences occur. The consequence of this combination of events is that primary repellents are excellent in stopping short-term consumption. But because of the failure of the repellents to function as strong unconditional stimuli, they fail to promote strong learned avoidance. The effect is to promote sampling behavior. In the wild, birds will quickly leave a resource defended with a primary repellent (Glahn *et al.*, 1989), presumably because the risk of danger of the resource patch is perceived to be high. However, these authors also found that if the primary repellent is removed, birds quickly return to the resource.

The effects of nociceptive primary repellents can also be modulated by other dietary constituents. For example, the coocurrence of sugar with the bird repellent methyl anthranilate diminishes the dose-dependent repellent effect of methyl anthranilate (Clark and Mason, 1993). This cross-modality antagonistic interaction between palatable taste cues and unpalatable nociceptive cues appears to be a widespread phenomenon. In humans and rats, endogenous opioid peptides and their agonists (e.g., morphine) increase the intake and preference of palatable sweet foods, whereas opioid antagonists (e.g., naltrexone) produce opposite effects (Le Magnen, 1992; Czirr and Reid, 1986; Fantino *et al.*, 1986). This morphine-like analgesia produced by ingesting sugars can raise the threshold for irritation and pain tolerance (Mercer and Holder, 1997; Blass and Shide, 1994; Blass *et al.*, 1987).

Fruits increase their sugar content as they mature, but the chemicals associated with avoidance are not necessarily withdrawn. Preliminary experiments with *Prunus* spp., *Cornus* spp., and *Morus* spp. indicate that avoidance of unripe fruits is associated with the presence of primary repellents (L. Clark, unpublished data). The palatability of fruits increases as sugar content increases during maturation, despite

the continued presence of the primary repellents. Thus, it appears that, at least for these species of plants, the timing of palatability of fruit is regulated via a sugar-induced analgesia of primary irritants.

Plants that have seeds that are animal-dispersed and that provide fruits as attractants require appropriate defenses against seed predation and untimely frugivory. Seeds dispersed before maturation clearly would not have high germination and survival potential. Plants generally possess physical or toxic chemical means to minimize seed predation. However, it would not be to the plant's advantage to possess potent toxicants in the fruit pulp, even in unripe fruit. One consequence of doing so might be long-term avoidance of its fruit by potential dispersers. Rather, it is to the plant's advantage to possess transient protection to fruits and to have birds return to the fruit at a later time when the seeds are ready for dispersal. This may be achieved by possessing chemicals that produce a mild toxicosis such that the learned avoidance is rapidly extinguished (Cipollini and Levey, 1997), or by possessing a chemical defense that does not promote learning and can be easily modulated with simple biochemical changes of the fruit (Clark, 1996). This hypothesis is consistent with the nature of avian frugivore foraging patterns. Birds will damage fruit by sampling throughout its development. At some point during fruit development, sampling damage gives way to consumption. Primary repellents are ideal chemical defenses for modulating the timing of frugivory because of their short-term repellent effects and the biochemical simplicity by which the chemical defense can be adjusted, i.e., the presence of sugars provides both the energetic incentive for frugivory and the biochemical means for the plant to neutralize its chemical defense against the frugivore/seed disperser.

7. IMPLICATIONS FOR WILDLIFE MANAGEMENT

Understanding the chemical ecology of birds and mechanisms underlying palatability has been critical in developing techniques to alter bird behavior for conservation and agricultural purposes. Conflicts between wildlife and humans occur on a regular basis (Conover *et al.*, 1995; Mason and Clark, 1992). At times wildlife causes significant damage to crops and structures. At other times human activity represents a threat to the well-being of wildlife populations. To resolve these conflicts a variety of techniques is employed (Hygnstrom *et al.*, 1994), among which are use of nonlethal chemical repellents (Mason and Clark, 1992). The most effective nonlethal chemical repellents for birds

are secondary repellents (e.g., Dolbeer *et al.*, 1994; Bullard *et al.*, 1983), but these compounds are generally toxic in nature (Thompson, 1988). Thus, application rates, harm to nontarget species, and human tolerance standards must be closely monitored. As a consequence, these compounds have highly restrictive constraints imposed upon their registration labels [United States Environmental Protection Agency-Federal Instecticide, Fungicide, and Rodenticide Act (EPA-FIFRA), 40 CFR 158.145].

The focus of research into primary repellents has been driven largely by practical considerations to find effective, nonlethal, environmentally benign repellents. Generally, the compounds considered for research purposes have been empirically elucidated, often being derived from natural plant products, many of which are used as human food flavor additives (Avery *et al.*, 1996; Watkins *et al.*, 1995; Mason and Bonwell, 1993; Crocker *et al.*, 1993; Avery and Decker, 1992; Jakubas *et al.*, 1992; Jakubas and Mason, 1991; Clark *et al.*, 1991; Mason *et al.*, 1991b; Mason, 1990; Mason and Otis, 1990; Mason and Turpin, 1990; Crocker and Perry, 1990; Bell and Harestad, 1987; Mason and Clark, 1987; Kare, 1961). This criterion does not necessarily imply environmental safety, because the quantities of materials used to achieve bird repellency and those used as flavor additives are often vastly different. However, because United States EPA registration costs are high for pesticides, these compounds are of interest because there already exist large amounts of data on toxicity and animal tolerance. This body of information represents a considerable cost savings to prospective registrants. Still, considerations of economy, production, formulation, regulation, and efficacy can eliminate a candidate repellent at any point in the development process. Relying on the serendipitous discovery of active agents severely constrains the likelihood that any compound will meet all the necessary development criteria (Mason and Clark, 1992). Indeed, in the United States there is currently only one compound registered as a bird repellent that functions as a primary repellent, methyl anthranilate (U.S. EPA registration numbers: 58035–6, 58035–7, 58035–9, 66550–1), and this compound took over 33 years to come to market. More systematic efforts to identify candidate bird repellents have been made recently (Clark and Shah, 1994, 1991a; Shah *et al.*, 1992, 1991; Clark *et al.*, 1991; Mason *et al.*, 1989). The molecular modeling efforts using the pharmacophore approach for rational repellent design are an attempt to prescreen candidate repellents and target for development only those compounds that have a high probability of surviving the gauntlet of economic, regulatory, and efficacy filters (Clark, 1997a).

7.1. Anthranilates: Current Uses

Methyl anthranilate is a natural plant product found in orange and jasmine blossoms, as well as in different varieties of grapes (Nelson *et al.*, 1977; Furia and Bellanca, 1975). To humans, this compound has a grapelike odor, which is the principal basis for its use as a food flavoring additive (Furia and Bellanca, 1975; U.S. FDA 21 CFR 170–99). Methyl anthranilate was first described as a bird repellent by Kare (1961). Recent studies suggest that methyl anthranilate repellency of birds is attributable to its chemesthetic qualities rather than to unpalatability associated with gustatory cues (Clark, 1996). In the field, formulations of methyl anthranilate have been used to reduce blackbird (Icterini) use of feed lots of cattle and swine (Mason *et al.*, 1991c, 1985; Glahn *et al.*, 1989); decrease avian depredation of fruit crops (Curtis *et al.*, 1995; Cummings *et al.*, 1995a; Askham, 1992; Avery, 1992; Askham and Fellman, 1989); decrease avian depredation of seed crops (Avery *et al.*, 1995); protect bird eggs from avian predators (Avery and Decker, 1994); protect orchids from bird damage (Cummings *et al.*, 1994); and reduce grazing on turf by geese (Mason and Clark, 1996a, 1995c, 1987; Cummings *et al.*, 1995b, 1992, 1991). Several studies have investigated the potential of formulations to decrease the risk of exposure of birds to cyanide by treating contaminated water in mine tailing ponds (Clark and Shah, 1993, 1991b); reduce the risk of incidental ingestion of white phosphorus by ducks using military artillery ranges in wetlands (Clark and Cummings, 1995, 1994); reduce the use of landfills by gulls (Vogt *et al.*, 1994); and reduce the risk of bird–aircraft collisions by decreasing the attractiveness of water to gulls in and around airports (Dolbeer *et al.*, 1993, 1992).

7.2. Good News–Bad News: Constraints and Future Directions for Primary Repellents

Despite the potential for success of methyl anthranilate or other active agents for use as conservation tools, several important considerations must be borne in mind. First, primary repellents are most effective when animals have alternative, palatable resources available to them. What the primary repellent does is to rerank the palatability of food items (*sensu* optimal foraging theory). If no alternative exists, birds may increase their tolerance to the irritation and pain levels experienced when they ingest the active agent. Pain perception and an animal's reaction to the perception of pain are based upon the motivational state of the animal (Melzack, 1973). By analogy, injuries sustained by

humans in sports and war are tolerated beyond levels caused by similar injuries incurred in more routine normal situations. Second, most application formulations are delivered orally. These formulations were designed to protect food resources, but, as discussed in earlier sections on mediating mechanisms, use for that purpose may be an inefficient means to get the active agent to the most sensitive avian receptor fields (mucous membranes in the nasal capsule or the eyes). Thus, because high vapor pressures are needed to achieve irritating levels via retronasal stimulation, higher concentrations of the active agent are required to produce the desired effect. Moreover, if birds do not ingest a topically treated resource, there will be no repellency. For example, geese may use lawns or turf in a variety of ways. Treatment of turf with formulations containing methyl anthranilate will prevent geese from grazing on the grass, and, if the underlying reason for their utilizing a site is foraging, they will quickly leave the site (Mason and Clark, 1995c). However, if they use the site for loafing, or if there is supplemental feeding by humans as might occur in many parklike situations, the efficacy of the repellent is diminished (Cummings *et al.*, 1995b). Thus, the formulation must be appropriate for efficiently targeting the mediating chemical receptors, but it must also be applied in a way that is appropriate to affect the expected objectionable behavior of the birds. Contact repellents may exist, but their efficacy and practicality are not well understood (Clark, 1997b). In many circumstances it may be desirable to achieve repellency before a bird comes in contact with the resource that is to be avoided. Toxic waste sites represent a threat to birds that land in them because of the high risk of percutaneous absorption of toxicant. Therefore, surface treatment of waste sites is inadvisable. Formulation and application strategies that employ repellent dispersion by aerosols or sprays may work to target efficiently the eyes and nasal passages of birds, cover large areas, and ward off the birds before they land on the toxic ponds. In effect, this is the use of bird tear gas for bird crowd control. Because the compounds have no effect on mammals and are highly safe for both birds and mammals, such strategies might prove useful in the future. These methods have only recently begun to be investigated (L. Clark, unpublished), and their utility and practicality have yet to be determined.

We are now at the point where identifying the active ingredient for a formulation is no longer the major obstacle to providing conservationists with nonlethal avian repellents. The major questions to be addressed in the future are technological and ecological in nature. From a technological perspective, formulation constraints are critical considerations. The formulation must deliver the repellent to the receptor sys-

tem that mediates the targeted behavioral response. A formulation must not interact with the repellent to render it inactive. For example, methyl anthranilate will bind tightly to charcoal or graphite and become essentially unavailable for release. These substrates are typically used as matrices in granular pesticides. Clearly, incorporating methyl anthranilate into a granular pesticide that is graphite-based would not reduce the risk of avian ingestion. Similarly, interaction of the repellent with any number of agricultural adjuvants can hinder the availability of the active agent to birds (Clark and Mezine, 1997), yet standard residue studies would indicate sufficient amounts of repellent remain on the crop. Without an understanding of the interaction of adjuvant and active agent, one might conclude from field studies that the repellent fails to achieve its goal, but to base the conclusion on the wrong reasons.

Ecological and behavioral considerations of the target system must be considered as well. Repellents act to alter the palatability of resources relative to other resources that are available. If no other resource is available, then primary repellents will fail. However, in most circumstances other resources are available, and the efficacy of the repellent is dictated by short-term costs associated with exploiting these resources.

The dearth of effective repellents has largely been a consequence of a fundamental lack of knowledge about the chemical and physiological bases influencing the behavior of birds. However, recent investigations have shown that the divergent areas of sensory biology, structural chemistry, physiology, and behavioral ecology can be interrelated and that if this information is used as part of an integrated management strategy, the identification and development of primary repellents is feasible. The identified technologies may be a safe means by which to alter bird behavior to the benefit of the species in question, but also to the benefit of humans.

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